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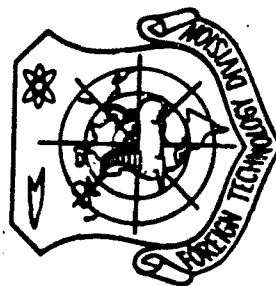
FOREIGN TECHNOLOGY DIVISION



THE TOXICITY AND THE NATURE OF THE ACTION
OF FLUORINATED ALCOHOLS
(TRIFLUOROETHANOL AND 1,1-DIHYDROPERFLUOROBUTANOL)

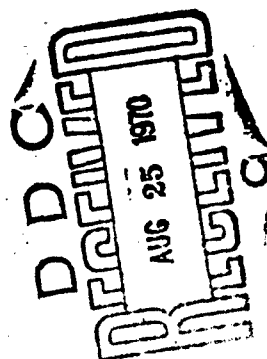
by

T. K. Nikitenko and M. S. Tolgskaya



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Perfluoride alcohols (dihydrofluorinated alcohols), a class of halogenated alcohols of the fatty acid series, find wide application in organic synthesis and production of plastics. They are colorless volatile heavy liquids soluble in alcohol and ether but poorly soluble in water. The chemical properties of these compounds depend upon both the hydroxyl group and the halogen. According to literature data, halogen derivatives of alcohols are strong toxins which affect the central nervous system and the metabolism; they also possess a significantly irritating effect (N. V. Lazarev).

Our task included a study of the toxic properties of trifluoroethanol ($\text{CF}_3\text{CH}_2\text{OH}$) and 1,1-dihydroperfluorobutanol ($\text{C}_4\text{F}_9\text{OH}$) alcohols. We could not find any information in the literature concerning the toxicity of the $\text{C}_4\text{F}_9\text{OH}$ alcohol. Regarding the toxicity of the trifluoroethanol, Ye. T. Lykhina and V. G. Ovcharov report that this substance in concentrations of 4-5 mg/l was fatal to mice in a period of 2 hours. On the basis of the results of this single effect and of calculation data, these authors recommend a maximum

permissible concentration (MPC) in the air of the industrial buildings at a level of 0.01 mg/l for trifluoroethanol and a level of 0.03 mg/l for dihydroheptafluorobutanol and dihydroheptafluoropropethanol, which are similar to it in structure. According to the experimental data of V. D. Bartenev the MPC for the tetrafluoropropene and octafluoroamyl alcohols in the air of industrial buildings comprises 0.02 mg/l.

Comparison of physicochemical properties of the simple and fluorinated alcohols confirms that trifluoroethanol and 1,1-dihydroperfluorobutanol have a molecular weight 2-3 times greater and a specific gravity approximately double that of the simple alcohols: they have a higher saturated vapor pressure and a considerably greater volatility.

Through experiments we established that the lethal concentrations of trifluoroethanol for a single 2-hour inhalation exposure for mice were LC_{84} 4.27 mg/l, LC_{50} 2.9 mg/l (2.28-3.39), and LC_{16} 1.99 mg/l; for 1,1-dihydrofluorobutanol, LC_{84} 15.14 mg/l, LC_{50} 10.23 (8.2-12.79), and LC_{16} 7.08 mg/l (the statistical calculation of the data was carried out by the Litchfield-Wilcoxon method). Comparison of the lethal concentrations of the fluorinated alcohols indicates that the trifluoroethanol is almost 4 times more toxic than 1,1-dihydroperfluorobutanol. The variability of the lethal concentrations (ratio of LC_{84} to LC_{16}) of the two alcohols is approximately the same and equals 2. The coefficient of the probability of inhalation poisoning (CPIP, i.e., the ratio of the volatility of the substance at 20° to the LC_{50} of mice during a 2-hour exposure period; I. V. Sanotskiy) is 164.2 for trifluoroethanol and 41.5 for 1,1-dihydroperfluorobutanol. As the CPIP shows, the danger of developing acute poisoning during inhalation of trifluoroethanol is approximately 4 times greater than during inhalation of 1,1-dihydroperfluorobutanol; the function of the slope S^* comprises 1.46 and 1.40, respectively.

* S or the function of the slope of the straight line of fatal concentrations to the abscissa axis is calculated by the formula:

$$S = \frac{\frac{CL_{45}}{CL_{15}} + \frac{CL_{45}}{CL_{15}}}{2} \text{ (Litchfield and Wilcoxon, 1949).}$$

The clinical pictures of intoxication during inhalation poisoning by trifluoroethanol and 1,1-dihydroperfluorobutanol are of the same type and are characterized by manifestations of a narcotic effect. Judging by the data of pathomorphological studies, the death of the animals during the exposure and the day after is caused by the expressed vascular disorder in the brain in the form of acute hyperemia, hemorrhages (Fig. 1), and phenomena of perivascular and pericellular edema. In the animals which died on days 2-5 dystrophic changes in the parenchymatous organs up to foci of necroses in them (Fig. 2) and also signs of irritation of the upper respiratory tract (swelling, desquamation, necrobiotic changes in the epithelium of the bronchials) were observed.

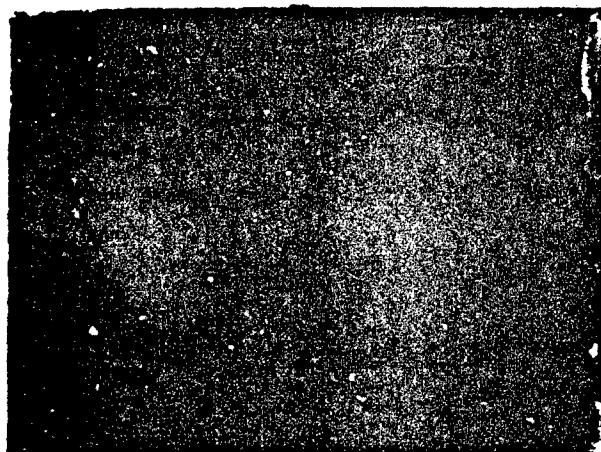


Fig. 1. Extensive hemorrhage in the mouse which died on the first day after a single inhalation exposure to 1,1-dihydroperfluorobutanol at 20 mg/l concentration. Marked swelling of the nerve cells. Nissel stain, mag. $\times 200$.

We determined the threshold concentrations of these alcohols by using rats during a single 4-hour inhalation exposure with respect to the change in the threshold of neuromuscular irritation, oxygen requirement, respiration rate, and the weight coefficients of the internal organs. The threshold concentrations of trifluoroethanol

fluctuate from 0.1 to 0.33 mg/l and those of 1,1-dihydroperfluorobutanol, from 1 to 1.5 mg/l.

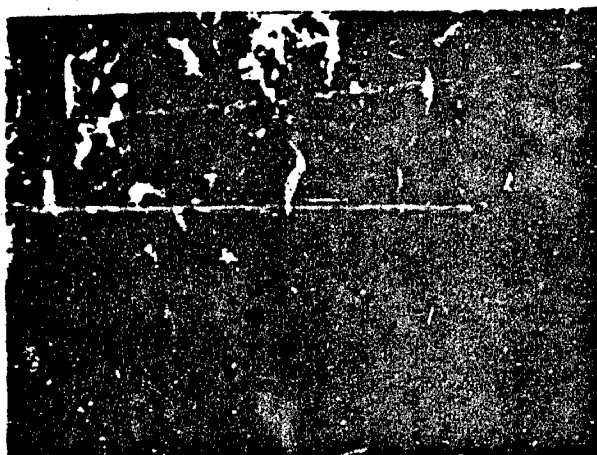


Fig. 2. Necrosis of the epithelium of convoluted tubules in the kidney of a mouse which died on the 3rd day after a single inhalation exposure to trifluoroethanol with a concentration of 2 mg/l. Hematoxylin-eosin stain, mag. $\times 140$.

Testing the comparative toxicity of trifluoroethanol and 1,1-dihydroperfluorobutanol when introduced into rats' stomachs, we found that the first is approximately 6-7 times more toxic (LD_{50} of trifluoroethanol equals 0.59 g/kg and that of 1,1-dihydroperfluorobutanol, 3.63 g/kg). The cumulation coefficient of trifluoroethanol during the introduction into the stomach using Lim method (Lim with co-authors) equals 2.4 (animals begin to die upon introduction of a dose 2 times greater than LD_{50} ; all animals die between the 12th and 18th day). Cumulative coefficient of 1,1-dihydroperfluorobutanol equals 2.28 (animals begin to die with a single introduction of a dosage close to LD_{50} ; all animals die between the 7th and the 25th day). The data presented confirms the fact that the fluorinated alcohols do not possess expressed cumulative properties.

A two hour contact of the skin of the tails of white mice (2/3 of their length) with trifluoroethanol and 1,1-dihydroperfluorobutanol

leads to pronounced local changes (hyperemia the first day, darkening and mummification the following day). Also revealed is a general toxic effect of trifluoroethanol, which causes death in 80% of the experimental animals; this indicates that the product penetrates the unbroken skin.

A single introduction of the alcohols into the conjunctival sacs of the eyes of rabbits causes catarrhal and in some cases catarrhal-suppurative conjunctivitis with a subsequent development of a permanent corneal opacity.

Considering the greater toxicity of the trifluoroethanol we carried out subacute and chronic inhalation poisoning of the animals only with this substance. The experiment showed that repeated inhalation exposure (4 weeks with daily 4-hour exposure) to trifluoroethanol at concentrations of 0.35 mg/l (approximately 1/10 of LC_{50}) leads to pronounced subacute intoxication of rats and guinea pigs. Part of the animals (4 rats out of 10 and 2 out of 6 guinea pigs) die in a period of 3-4 weeks with a picture of acute loss in weight (by 40-60 g in comparison with the initial weight and weight of the control group); a decrease in hemaglobin of 3-4 mg% in comparison with the control group; a decrease in the number of erythrocytes in the peripheral blood and decrease in the amount of hippuric acid in the urine after loading with sodium benzoate. Analogous statistically reliable disturbances were noted at the end of the experiment in animals that survived intoxication.

The pathomorphological changes are characterized by the plethora of the tissues of the lungs, liver, kidneys, and especially the brain; it was sharply expressed in the animals which died. In the lungs the signs of poorly expressed bronchitis, focal thickening of the alveolar septi, and in the dead animals small foci of catarrhal pneumonia were observed. In the brains of all animals we detected the phenomena of perivascular and pericellular edema, swelling of the protoplasm of cells of the cortex and of the subcortical ganglia with the formation of small vacuoles, and hyperplasia of the

microglial elements. The liver and kidneys showed dystrophic changes which were not sharply expressed.

In the chronic experiment in a period of 4 months we tested 2 concentrations of trifluoroethanol: an average of 0.12 mg/l (equal to the threshold of the acute effect) and 0.06 mg/l (with fluctuations in the chamber from 0.01 to 0.09 mg/l). It was established that the higher concentration (0.12 mg/l) is effective in chronic inhalation. The character of the change in the animals is analogous to that in the subacute experiments we carried out earlier. From the 2nd month of intoxication the rats and guinea pigs exhibited retardation in gain of body weight. At the end of the experiment an increase in the neuromuscular threshold of irritability was recorded; this confirms the prevalence of inhibition processes in the central nervous system and decreases in the hemoglobin level and the amount of erythrocytes in the peripheral blood and the content of hippuric acid in the urine after loading with sodium benzoate. These changes are statistically reliable towards the end of the 4th month of intoxication. A month after the termination of the experiment a tendency toward restoration of the disrupted functions was noted.

In the animals subjected to the action of trifluoroethanol in a concentration of 0.06 mg/l reliable changes with respect to the above-listed indices; only an increase in the body weight of the experimental animals (in comparison with the control group) in the 4th month of intoxication was noted.

In the histological examination of animals sacrificed at the end of the experiment, evidence of irritation in the upper respiratory tract (rhinitis, trachitis, and bronchitis) and dystrophic changes in pyrenchymatous organs were noted (Fig. 3). These changes were more expressed in the animals which were subjected to the action of trifluoroethanol in large concentrations (0.12 mg/l). In animals which were subjected to inhalation of trifluoroethanol at a concentration of 0.06 mg/l the pathomorphological changes principally carry a compensatory adaptive character (hyperplasia of cells of the reticulo-endothelial system).

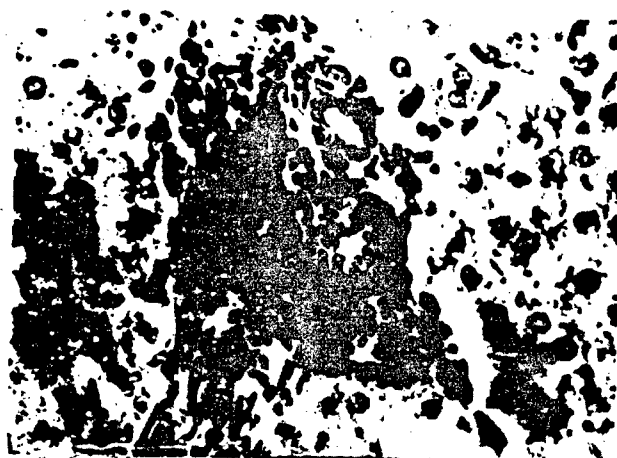


Fig. 3. Rat liver. Hyperplasia of the reticulo-endothelial elements with formation of histiocytic nodules during chronic inhalation exposure to trifluoroethanol at a concentration of 0.12 mg/l. Hematoxilin-eosin stain, mag. $\times 140$.

Judging by the results of the experimental investigations, trifluoroethanol at a concentration of 0.12 mg/l and higher can cause chronic poisoning; a concentration close to 0.06 mg/l is the threshold of the chronic action.

Considering the high volatility of the trifluoroethanol (481 mg/l), high CPIP (164), and the narrowness of the zone of the chronic effect (1.7), we found that in going from threshold to maximum permissible concentrations the safety factor must equal approximately 6. The MPC of the trifluoroethanol in the air of industrial quarters comprises 10 mg/m^3 (in the norms on this substance we must note that it penetrates unbroken skin).

The MPC of 1,1-dihydroperfluorobutanol, which is less toxic as compared with trifluoroethanol irritation effect threshold close to 0.3 mg/l (by analogy with pentafluoropropyl and other alcohols) comprises 20 mg/m^3 .

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13. ABSTRACT <i>discusses</i> The paper carries materials elucidating the toxic action of fluorated alcohols (trifluoroethanol and 1,1-dihydroperfluorobutanol) with different routes of their access into the organism of experimental animals. The fluorated alcohols under study are shown to be toxic compounds. Topical irritating action at the site of their application and general toxic effect of these poisons, characterized by manifestations of their narcotic action on the central nervous system and by dystrophic changes in parenchymatous organs, were revealed. Maximum permissible concentrations of their fumes in the air of industrial premises have been established, which for trifluoroethanol is 10 mg/m ³ and for 1,1-dihydroperfluorobutanol - 20 mg/m ³ . [AP0043900] <i>and</i> <i>in</i>			

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